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Regional Distribution of Cardiac Output at Rest and During Exercise in Patients With Exertional Angina Pectoris Before and After Nifedipine Therapy

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The short-term effects of sublingual nifedipine (20 mg) on cardiac output and its distribution at rest and during exercise were evaluated by measurement of iliofemoral blood flow and cardiac output in 10 men with stable angina pectoris controlled by metoprolol. At rest, nifedipine significantly decreased iliofemoral vascular resistance from 294 ± 36 to 165 ± 29 dynes·s·cm^{-5}·10^{2} ($p < 0.01$) and significantly increased iliofemoral blood flow from 0.34 ± 0.04 to 0.57 ± 0.11 liters/min ($p < 0.05$). Systemic vascular resistance was reduced from 19 ± 1 to 13 ± 1 dynes·s·cm^{-5}·10^{2} ($p < 0.001$) and cardiac output increased significantly from 4.7 ± 0.3 to 5.8 ± 0.5 liters/min ($p < 0.05$). Mean arterial pressure decreased significantly and heart rate increased significantly.

During maximal upright bicycle exercise during nifedipine therapy, iliofemoral vascular resistance and leg blood flow were unchanged compared with control (23 ± 2 versus 21 ± 3 dynes·s·cm^{-5}·10^{2} and 4.7 ± 0.5 versus 4.4 ± 0.6 liters/min), cardiac output remained significantly increased (12.8 ± 0.8 to 15.2 ± 1.2 liters/min, $p < 0.05$) and systemic vascular resistance remained significantly reduced (8 ± 1 to 5 ± 1 dynes·s·cm^{-5}·10^{2}; $p < 0.001$). The proportion of cardiac output distributed to the working lower limbs was significantly reduced at all exercise levels.

In summary, nifedipine caused a redistribution of cardiac output by vasodilating nonexercising vascular beds without altering the locally mediated vasodilation in exercising muscle. In patients with coronary artery disease given nifedipine therapy, an increase in exercise tolerance is due to relief of myocardial ischemia rather than to increased peripheral oxygen delivery.

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The magnitude and distribution of cardiac output change markedly from rest to exercise, largely because of the increase in exercising muscle blood flow (1–4). Antianginal medications with vasodilating properties may not only increase cardiac output but may also alter its distribution. The calcium channel blocker nifedipine is a powerful arterial vasodilator (5–7) and has been shown to increase cardiac output at rest and during exercise (8–10). If the normal distribution of cardiac output is maintained after nifedipine, exercising muscle blood flow should increase, thereby reducing fatigue and potentially increasing exercise tolerance.

Muscle blood flow increases at rest after nifedipine (11,12). However, indirect calculations of muscle blood flow during exercise after nifedipine have shown an increase in oxygen extraction in femoral venous blood suggesting a reduction of flow (13). This increased oxygen extraction was associated with increased leg fatigue and no change in exercise tolerance.

The purpose of this study was to determine whether nifedipine alters the distribution as well as the magnitude of the cardiac output response to exercise by direct measurement of exercising muscle blood flow and cardiac output in patients with exertional angina pectoris.

Methods

Study patients. Ten male patients (mean age 52 years, range 43 to 68) were studied within 1 week of coronary arteriography. All patients had a history of exertional chest

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defect. Seven patients had single vessel disease and three had two vessel disease. Mean ejection fraction was 67% (range 60 to 74%). No patient had significant valvular heart disease or significant lower limb arterial disease. Long-term metoprolol therapy (100 to 200 mg/day) for angina was continued in all patients. The protocol was approved by the ethics review committee at this institution and all patients gave written informed consent to the study.

Study protocol. The study was designed as an open within-patient evaluation of the hemodynamic and metabolic effects of a single sublingual dose of nifedipine at rest and during upright bicycle exercise. The protocol was usually undertaken the day after coronary arteriography. After patients had been familiarized with the laboratory exercise equipment, a 7F Swan-Ganz thermodilution catheter was inserted into an antecubital vein and positioned in the pulmonary artery. A 21 gauge polyethelyene cannula was inserted into a radial artery. A 5F thermodilution catheter was inserted percutaneously into a femoral vein and the infusion port positioned 1 cm above the pubic ramus. The positions of both thermodilution catheters were checked with fluoroscopy.

Thirty minutes later the patients were positioned on an upright bicycle ergometer (Siemens-Elema model 380B) and after another 20 min, baseline hemodynamic and metabolic variables were measured. The zero reference point for pressure was set at the fourth intercostal space in the midaxillary line. Phasic and mean systemic arterial, pulmonary artery, pulmonary artery wedge and right atrial pressures (Bell and Howell 4-327-1 transducers) were recorded on an Electronics for Medicine VR12 recorder.

Blood samples were obtained from the radial artery and femoral vein for measurement of oxygen saturation, lactate concentration and hemoglobin and from the pulmonary artery for measurement of oxygen saturation and hemoglobin.

After rest measurements were made, patients began exercising with an initial work load of 30 W. The work load was increased by 20 W every 4 min until symptoms prevented further exercise. All exercise tests were performed ≥4 h after a light breakfast. Blood flow and cardiac output measurements were made during the 2nd and 3rd min of each exercise level. Pressure measurements and blood samples were taken during the 4th min.

After the termination of exercise, patients dismounted the bicycle and rested for ≥1 h. They were then repositioned on the bicycle ergometer and rested until hemodynamic variables had returned to control rest values. Nifedipine was then administered sublingually (20 mg). After ≥1 more hour, the rest measurements and exercise protocol were repeated. Measurements were made at identical times as in the control study and if the patient exercised longer on nifedipine therapy, also at the new maximal level.

Methodologic studies. Femoral vein flow was measured with a 5F thermodilution catheter (with the thermistor at 1.5 cm and injection port at 10 cm from the tip), a thermodilution computer (American Edwards model 9520A) and a 2.4 ml bolus of iced 5% dextrose. This system was evaluated using an open loop system in which 37°C water was continuously pumped through 7 mm internal diameter polyethylene tubing. Flow measured by the thermodilution system correlated ($r = 0.99$) with directly measured flow rates from 0.2 to 8.0 liters/min with an SE of 0.17 liter (Fig. 1). To maximize the number of femoral flow measurements, 4 min exercise stages were used in this study. A mean of 4.5 femoral flow measurements was obtained at rest and 5.5 measurements were obtained per exercise stage. The mean coefficient of variation for femoral flow measurements was 16% at a mean work load of 63 W. To promote mixing of the indicator, a specially designed injector was used to deliver the 2.4 ml of injectate in <300 ms. No adverse effects of rapid injection were observed. Rest and exercise leg flow measurements obtained using this technique were similar to those using other methods (14–16).

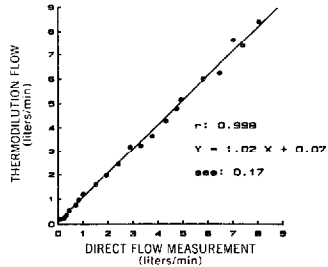

Figure 1. Comparison of flow determined by timed direct measurement (abscissa) and thermodilution (ordinate) using a 5F catheter, 2.4 ml injectate and thermodilution computer.

Measured variables and calculations. Hemoglobin, oxygen saturation, pH and oxygen and carbon dioxide tensions were measured in each blood sample (Co-Oximeter, Instrumentation Laboratories Model 282, Corning 175 Blood Gas Analyser). Blood oxygen content was calculated as the product of hemoglobin concentration, 1.39 ml oxygen of hemoglobin and the percent oxygen saturation. Cardiac output was measured in triplicate by bolus thermodilution with a cardiac output computer (Instrumentation Lab. Model 701). Total and leg oxygen consumptions were calculated using the Fick equation from the product of cardiac output or femoral flow and the arteriovenous oxygen difference across the pulmonary or leg vascular bed, respectively. Oxygen consumption measured directly and calculated using

Table 1. Effects of Nifedipine on Systemic Hemodynamics and Metabolic Responses to Exercise in 10 Patients

	HR (beats/min)	MAP (mm Hg)	CO (liters/min)	PAWP (mm Hg)	TPR (dynes·s·cm^{-5}·10^2)	$\dot{V}O_2$ (liters/min)	O$_2$ext (%)
Control							
Rest	67 ± 3	110 ± 4	4.71 ± 0.30	5.5 ± 1.3	19 ± 1	0.25 ± 0.02	26.5 ± 1.7
30 W	86 ± 3	126 ± 4	7.68 ± 0.39	13.5 ± 1.9	13 ± 1	0.63 ± 0.04	42.3 ± 3.7
50 W	93 ± 4	130 ± 4	8.99 ± 0.43	16.6 ± 2.6	11 ± 1	0.84 ± 0.07	46.9 ± 3.3
Max	124 ± 8	131 ± 4	12.76 ± 0.78	22.7 ± 3.2	8 ± 1	1.60 ± 0.17	61.7 ± 3.4
Nifedipine							
Rest	85 ± 5*	91 ± 3†	5.77 ± 0.51‡	5.3 ± 1.0	13 ± 1*	0.24 ± 0.02	21.2 ± 1.9*
30 W	98 ± 5‡	104 ± 3*	10.17 ± 0.68†	10.0 ± 1.2‡	8 ± 1*	0.72 ± 0.05‡	36.7 ± 3.0‡
50 W	107 ± 5†	106 ± 3*	11.67 ± 0.94‡	10.7 ± 1.4‡	7 ± 1*	0.92 ± 0.03	41.3 ± 2.9†
Max	139 ± 7†	105 ± 5†	15.24 ± 1.21‡	15.2 ± 2.9‡	6 ± 1*	1.81 ± 0.20	59.3 ± 3.8

*$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$ versus corresponding level during control exercise test. Data are mean ± SEM. CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; Max = maximal; O-ext = systemic oxygen extraction; PAWP = pulmonary artery wedge pressure; TPR = total peripheral resistance; $\dot{V}O_2$ = maximal oxygen consumption.

the Fick equation correlates well in this laboratory (13). Lactate production was calculated as the product of femoral vein flow and the leg arteriovenous lactate difference. Blood for lactate determination was deproteinated in perchloric acid and assayed by a spectrophotometric technique. Normal values for our laboratory using this technique are <1.5 mmol/liter. Iliofemoral vascular resistance was derived from mean systemic and right atrial pressure minus the pressure of a column of blood from the fourth intercostal space to the inguinal ligament divided by iliofemoral flow. Three ECG leads (aVF, V_1, V_5) were continously monitored and ST segment deviations were measured 80 ms after the J point (CASE II, Marquette Electronics).

Statistical methods. Data are presented as mean ± SEM. Differences between measurements at rest and at each exercise level are compared using paired Student's *t* tests. A p value of <0.05 was considered significant.

Results

Systemic Hemodynamic and Metabolic Measurements (Table 1)

Control. At rest, cardiac output was 4.71 ± 0.30 liters/min, mean wedge pressure was 5.5 ± 1.3 mm Hg and rest heart rate was 66.5 ± 3.4 beats/min, consistent with normal ventricular function and betablockade at rest. Systemic oxygen extraction was 26.5 ± 1.7% and total oxygen consumption was 0.25 ± 0.02 liters/min.

At a submaximal level of exercise (50 W, achieved by all patients), cardiac output had increased to 8.99 ± 0.43 liters/min and wedge pressure had increased to 16.6 ± 2.6 mm Hg.

Patients exercised for an average of 20.3 ± 2.0 min until stopped by chest pain. Maximal oxygen consumption ($\dot{V}O_2$) was 1.60 ± 0.17 liters/min at a maximal work load of 106 ± 9 W. Cardiac output reached a peak of 12.76 ± 0.78 liters/min with the wedge pressure at 22.7 ± 3.2 mm Hg. Systemic oxygen extraction increased to 61.7 ± 3.4% and arterial lactate increased from 0.50 ± 0.07 at rest to 5.71 ± 0.74 mmol/liters at peak exercise. Maximal ST segment depression was 3.1 ± 0.6 mm.

Effect of nifedipine. Administration of nifedipine led to an increase in rest cardiac output from 4.71 ± 0.30 to 5.77 ± 0.51 liters/min ($p < 0.05$) and a decrease in systemic oxygen extraction from 26.5 ± 1.7 to 21.2 ± 1.9% ($p < 0.001$). At submaximal exercise (50 W), cardiac output remained significantly increased; wedge pressure was decreased from 16.6 ± 2.6 to 10.7 ± 1.4 mm Hg ($p < 0.05$) (Table 1). Total peripheral resistance was correspondingly reduced from 11 ± 1 to 7 ± 1 dynes·s·cm^{-5}·10^2 ($p < 0.001$).

After nifedipine, three patients were able to exercise longer, but two others were limited by leg fatigue at a lower work level. Seven patients reported less chest pain with nifedipine. Mean exercise time increased to 21.1 ± 1.3 min (p = NS) and the mean maximal work load to 110 ± 6 W (p = NS). At peak exercise, cardiac output was significantly increased to 15.2 ± 1.2 liters/min ($p < 0.05$) and total peripheral resistance was correspondingly significantly reduced to 8 ± 1 to 6 ± 1 dynes·s·cm^{-5}·10^2 ($p < 0.001$). Wedge pressure was significantly reduced to 15.2 ± 2.9 mm Hg ($p < 0.05$) compared with control. The mean maximal $\dot{V}O_2$ remained unchanged at 1.81 ± 0.20 liters/min. Maximal ST segment depression was reduced to 2.7 ± 0.7 mm. Peak arterial lactate did not change significantly with nifedipine (5.71 ± 0.74 versus 6.66 ± 0.75 mmol/liter).

Leg Blood Flow and Metabolism (Table 2)

Control (Fig. 2 and 3). At rest, leg blood flow was 0.34 ± 0.04 liters/min, femoral oxygen extraction was 42.6 ± 2.4% and there was minimal lactate consumption in the leg (5.80 ±

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Table 2. Effects of Nifedipine on Leg Hemodynamic and Metabolic Responses to Exercise in 10 Patients

	Leg Flow (liters/min)	Leg $\dot{V}O_2$ (ml/min)	FVR (dynes·s·cm^{-5}·10^2)	O_2ext (%)	Lactate (mmol/liter)	Lact Prod (mmol/min)
Control						
Rest	0.34 ± 0.04	29 ± 3	294 ± 36	42.6 ± 2.4	0.52 ± 0.09	−0.01 ± 0.04
30 W	2.54 ± 0.21	282 ± 14	40 ± 3	56.6 ± 3.3	1.34 ± 0.18	0.80 ± 0.32
50 W	2.96 ± 0.24	372 ± 27	35 ± 3	61.2 ± 3.2	1.93 ± 0.38	1.13 ± 0.51
Max	4.67 ± 0.47	672 ± 80	23 ± 2	70.8 ± 3.1	6.50 ± 0.72	3.89 ± 0.90
Nifedipine						
Rest	0.57 ± 0.11*	40 ± 9	164 ± 29†	35.0 ± 3.5	0.55 ± 0.10	0.04 ± 0.05
30 W	2.44 ± 0.28	285 ± 40	36 ± 3	59.2 ± 4.4	1.57 ± 0.24	1.00 ± 0.40
50 W	3.04 ± 0.37	374 ± 37	29 ± 3	63.2 ± 3.4	2.09 ± 0.36	0.65 ± 0.51
Max	4.36 ± 0.58	651 ± 76	21 ± 3	75.9 ± 2.7	7.68 ± 0.96	5.78 ± 0.99*

*$p < 0.05$, †$p < 0.01$ versus corresponding level during control exercise test. Data are mean ± SEM. FVR = iliofemoral vascular resistance; Lactate = iliofemoral venous lactate; Lact Prod = iliofemoral lactate production; O_2ext = iliofemoral oxygen extraction; other abbreviations as in Table 1.

37.6 μmol/min). Leg $\dot{V}O_2$ was 29 ± 3 ml/min (11.5% of the total oxygen consumption). During submaximal exercise (50 W), leg flow increased to 3.0 ± 0.2 liters/min and leg oxygen extraction increased to 61.2 ± 3.2%.

At maximal exercise, peak leg blood flow was 4.67 ± 0.47 liters/min and leg $\dot{V}O_2$ increased to 672 ± 80 ml/min (42.1% of total $\dot{V}O_2$). Lactate metabolism in the leg changed from minimal consumption at rest (6 μmol/min) to a peak production of 3.89 ± 0.90 mmol/min, consistent with anaerobic metabolism. Changes in leg flow correlated with changes in total oxygen consumption ($r = 0.81$) (Fig. 3).

Effect of nifedipine (Fig. 2). Administration of nifedipine caused a modest increase in leg blood flow at rest from 0.34 ± 0.04 to 0.57 ± 0.11 liters/min ($p < 0.05$) consistent with the proportionate reduction in iliofemoral vascular resistance from 294 ± 36 to 164 ± 29 dynes·s·cm^{-5}·10^2 ($p < 0.01$). During submaximal exercise (50 W) with nifedipine, there was no significant change in leg blood flow or oxygen extraction in femoral blood and lactate production was also unchanged. At maximal exercise with nifedipine, leg blood flow was similar to control values (4.36 ± 0.58 versus 4.67 ± 0.47 liters/min respectively). Also, oxygen extraction, and therefore leg $\dot{V}O_2$ was unchanged. Peak leg $\dot{V}O_2$ was 36.0% of total $\dot{V}O_2$. Lactate production was significantly increased and peaked at 5.78 ± 0.99 mmol/min ($p < 0.05$ versus control).

Regional distribution of cardiac output (Fig. 4). In the control study at rest, mean muscle blood flow (calculated as twice the leg blood flow) was 15.3 ± 2.5% of the cardiac output. At submaximal exercise (50 W) this had increased to 66.3 ± 5.0% and at maximal exercise the proportion had reached 73.6 ± 5.8%. Nifedipine increased rest leg flow and cardiac output and there was a small but significant increase in the proportion of cardiac output going to the legs at rest to 21.2 ± 4.8% ($p < 0.05$). Submaximal leg flow was unchanged and the increased cardiac output decreased the proportion of cardiac output flowing to the legs to 51.6 ± 3.4% ($p < 0.001$). Similarly, at maximal exercise with nifedipine, the leg blood flow was unchanged whereas the cardiac output was significantly increased, resulting in a significant decrease in the proportion of cardiac output going to the exercising lower limbs to 57.6 ± 6.1% ($p < 0.05$). Therefore, nifedipine resulted in a significant redistribution of cardiac output at rest and during all exercise levels.

Discussion

Effect of nifedipine on central and leg hemodynamics. This study shows that nifedipine does not increase exercising muscle blood flow despite a significant increase in cardiac output. If exercise tolerance improves with nifedipine, it may be due to reduced myocardial ischemia from improved central hemodynamics. The central hemodynamic changes produced by nifedipine in this study were similar to those reported by us (10,13) and others (6,8,9). Both at rest and during exercise, nifedipine reduced total peripheral resistance and arterial pressure and increased heart rate and cardiac output. These changes were accompanied by less ST segment depression and a significantly lower pulmonary wedge pressure.

At rest, the changes in leg hemodynamics were similar to systemic changes. Leg blood flow increased with nifedipine and there was a corresponding decrease in iliofemoral oxygen extraction. Iliofemoral vascular resistance decreased to a similar extent as total peripheral resistance. In contrast, during exercise, leg blood flow did not increase above control values and leg $\dot{V}O_2$ was unchanged. Iliofemoral vascular resistance did not change during exercise with nifedipine. Therefore, most of the decrease in total peripheral resistance associated with nifedipine therapy is due to a decrease in resistance in nonexercising vascular beds. Because leg blood flow did not change during exercise, the increased cardiac output is directed through the vasodilated nonexercising tissues.

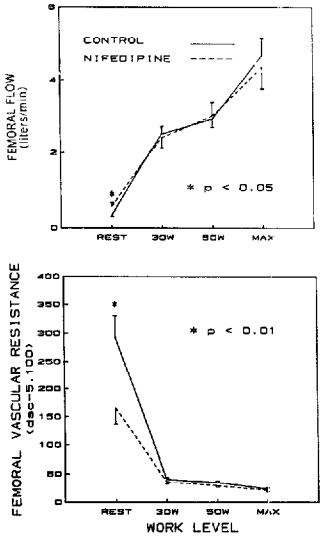


Figure 2. Effect of nifedipine on iliofemoral blood flow (upper) and iliofemoral vascular resistance (lower). Asterisks mark the significant differences between control and nifedipine data. dsc = dynes·s·cm; MAX = maximal.

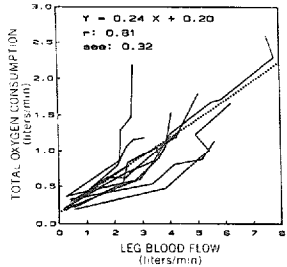


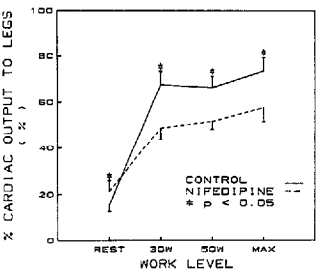
Figure 3. Relations between leg blood flow and total oxygen consumption in the control study. Continuous lines represent individual data in 10 patients. The dotted line represents the regression equation. Leg blood flow increased with maximal oxygen consumption except at the highest work loads when there was increased oxygen extraction.

During exercise in normal subjects, blood flow to nonexercising tissues is reduced because of constriction of resistance vessels mediated by the sympathetic nervous system (1,2,4). In our patients, blood flow to nonexercising tissues increased. Nifedipine appears to antagonize the physiologic vasoconstrictor effects of increasing sympathetic stimulation in nonexercising tissues during progressive exercise (17) without augmenting the physiologic vasodilation in working muscle.

Limitations. *Blood flow measurements.* Thermodilution has been used by several investigators to measure leg blood flow during exercise (14–16,18,19). However, this technique measures total limb flow, including that of nonexercising tissues. Most rest leg blood flow is probably directed to nonmuscular tissue and would have contributed to the significant increase in limb flow at rest after nifedipine. During exercise, nonexercising tissue blood flow is relatively much less. If nifedipine does significantly increase nonexercising muscle blood flow in the leg during exercise as it does elsewhere, there may have been a reduction in exercising muscle blood flow with nifedipine. This redistribution of blood flow within the leg would be consistent with the tendency for increased leg oxygen extraction and leg fatigue after nifedipine.

Study design and drug effects. We are aware of the limitations in interpreting the findings of such short-term single dose studies and the obvious order effect introduced

Figure 4. Effect of nifedipine on the mean percentage of cardiac output distributed to exercising muscle. Asterisks mark the significant differences between control and nifedipine data.



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by giving the drug after control observations, but with the experimental design, reversing the order would lead to carryover drug effects. Patients continued on metoprolol treatment for exertional angina. Beta-blockade is reported (20) not to interfere with exercise-induced vasodilation in muscle or to alter leg blood flow during exercise.

Physiologic implications. Muscle vascular resistance decreases markedly at the beginning of exercise. In the control study at the initial work load of 30 W, the iliofemoral vascular resistance decreased 86% and at maximal exercise it decreased 92%. In the nifedipine study, vasodilation due to nifedipine decreased iliofemoral vascular resistance by 44% at rest. In contrast, during exercise after nifedipine, there was no significant difference in iliofemoral resistance, suggesting that the local vasodilator responses to exercise are not further augmented by nifedipine.

Clinical implications. In patients with exertional angina who are given nifedipine therapy, any increase in exercise tolerance is not due to increased oxygen delivery to exercising muscle despite an increased cardiac output. The mechanism of action is by relief of myocardial ischemia rather than increased peripheral oxygen delivery.

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